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Genetics of Electrophysiology: Linking Genes, Brain, and Behavior

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Despite the extensive information about the heritability of behavioral traits, very little is known about the specific genes that are involved and the mechanisms of their influence on behavior. Classical (biometrical) behavioral genetic approaches establish a direct statistical link between genetic factors and behavior, while bypassing the intermediate level of analysis. Vogel (1981) has argued that a neurobiological approach aimed at identifying specific genes and mechanisms of their action in the nervous system has greater explanatory power than the biometrical approach, in which the pathway from gene to behavior necessarily remains a "black box." In this article, we propose that by studying individual differences in central nervous system functioning, researchers may learn about the neurobiological mechanisms that mediate genetically determined differences in behavior. We review studies from a relatively new branch of behavioral genetics—genetic psychophysiology—an area that may help elucidate the brain pathways mediating genetic influences on behavior.

Table 1 illustrates the evolution of the main problem addressed by behavioral geneticists. To date, studies aimed at the demonstration and assessment of genetic influences have achieved their goal, and the importance of genetics for various aspects of human behavior hardly is a matter of discussion any longer. Now, more specific questions are on the agenda: Which brain mechanisms mediate genetic influences on complex behavior, and which specific genes are involved? Advances in the methods of genetic analysis of complex traits, especially methods for detecting genes with relatively small effects, allow direct searches for genes involved in complex behaviors.

However, complex traits are likely to be influenced by multiple neurobiological components, each of which may be influenced by independent genes, which makes the task of identifying the effects of single genes on behavior very complicated. It may be easier to identify the effect of a gene on a more elementary neurobiological trait than to identify its effect on a complex behavior.

Recommended Reading

Deary, I.J., & Caryl, P.G. (1995). Intelligence, EEG, and evoked potentials. In P.A. Vernon (Ed.), *Biological approaches to the study of human intelligence* (pp. 259–315). Norwood, NJ: Ablex.

Niedermeyer, E., & Lopes de Silva, F. (1993). *Electroencephalography: Basic principles, clinical applications and related fields* (3rd ed.). Baltimore: Williams & Wilkins.

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INDIVIDUAL DIFFERENCES AND BRAIN ELECTRICAL ACTIVITY

Advances in neuroscience and psychophysiology have broadened knowledge about the physiological basis of human behavior and provided powerful tools for the assessment of brain function and structure. Such tools include neurophysiological techniques like electroencephalography and neuroimaging methods like positron emission tomography and magnetic resonance imaging. Genetic research imposes on such methods specific requirements, the most important of which are noninvasiveness and availability for the study of large samples including hundreds of subjects. So far, only electrophysiological techniques can meet these requirements. The two major methods for investigating brain function with electrophysiology are the electroencephalogram (EEG) and the event-related potential (ERP).

An EEG is recorded from electrodes placed on the scalp and depicts the spontaneous electrical activity of the brain. Commonly, the EEG activity is analyzed into its component rhythms, such as the alpha band of 8 to 12 cycles per second. Quantification usually consists of measuring the power associated with each rhythm, a measure yielded by Fourier analysis[2] of the EEG. This procedure yields *frequency spectra,* which plot EEG power for the various rhythms (*frequency bands*) at different electrodes. These measures of EEG power can be used as indices of the absolute and relative activation of different cortical areas.

EEG coherence refers to the association between the EEG powers at different recording sites (measured as a cross-correlation between the EEG signals from two scalp locations). It has been suggested that coherence measures the number and the strength of connections between different brain areas. The EEG parameters of power and coherence are associated with both normal and abnormal individual differences in behavior. For example, peak frequency of the EEG alpha rhythm and the degree of

Table 1. *Evolution of the main question in behavioral genetics*

Question	Goal
Do genes affect behavior?	Demonstration of genetic influences
To what extent do genes affect behavior?	Assessment of heritability
How do genes affect behavior?	Elucidation of mediating neurobiological mechanisms
What specific genes affect behavior?	Identification of specific genes

functional connectedness among distant cortical areas during mental activity are predictive of performance in cognitive tasks and even of general intelligence (Anokhin & Vogel, 1996). Other EEG features are associated with personality, in particular, with the basic dimensions of temperament described by Cloninger, Svrakic, and Przybeck (1993). An ongoing study (Anokhin, Vedeniapin, Rohrbaugh, Sirevaag, & Cloninger, 1997) has linked electrical activity in specific brain areas to high levels of harm avoidance (pessimism and anticipatory worry), low levels of self-directedness (feelings of helplessness, lack of goal direction, and inertia), and high levels of cooperativeness and novelty seeking.

The ERP is the brain's electrical response to the occurrence of a specific event. The event is usually a stimulus, a word or picture presented on a display or a tone presented through headphones, but the event can also be generated internally. The intention to move a limb, for instance, will generate an ERP known as the readiness potential. In general, the different ERPs are defined by a combination of their time of occurrence, their typical electrical waveform, the distribution of that waveform over the various areas of the brain, and the response of the ERP waveform to characteristics of the stimulus or task. Some ERPs occur within 10s of milliseconds after the event; others are prolonged and may last up to several seconds. The very early ERPs are influenced mainly by the physical characteristics of the stimulus. They are used to study the nervous pathways that transmit the incoming information to the sensory areas in the brain. ERPs in the 50- to 200-ms range are used to study the effects of arousal and attention on (automated) information processing. Late ERPs are determined by the interaction between the eliciting events and task demands, and reflect working memory and controlled information processing.

In ERP research, it is well known that the average extent of the electrical response in microvolts (the ERP amplitude) and the time of its peak (the ERP latency) can vary across individuals. Sometimes individual differences in ERP amplitudes and latency have been regarded as nuisance variables. They needed to be averaged to uncover the general structure of human information processing. More recently, however, these individual differences have become a research target per se. An ERP component called P300 provides the best example. The P300 is a wave that occurs about 300 ms after a relevant stimulus. Its latency and amplitude have been used to assess the speed of stimulus evaluation and the resources recruited during this process. Reliable within-subject stability over time has been established for both amplitude and latency of this component. Individual differences in the P300 have been associated with superior memory performance and the ability to allocate and maintain attention. The P300 is now the prime measure used in studies of normative cognitive aging (Polich, 1996) and susceptibility to alcoholism (Begleiter & Porjesz, 1995).

Thus, individual differences in EEG and ERP indices can be assessed reliably and are associated with psychological traits, cognitive function and dysfunction, and psychopathology. If interindividual variability in EEG and ERP indices is also heritable, these traits would be a powerful tool to bridge the gap between genes and behavior.

INDIVIDUAL DIFFERENCES IN BRAIN ELECTRICAL ACTIVITY ARE HERITABLE

The genetic aspects of the EEG have been investigated since the 1930s (reviewed in van Beijsterveldt & Boomsma, 1994). Taken together, twin and family studies convincingly demonstrate a high heritability of spontaneous electrical activity of the brain across a variety of conditions, including sleep, resting wakefulness, sensory stimulation, and performance of various tasks. Individual differences in EEG changes elicited by drugs (in particular, alcohol) also appear to be controlled by genetic factors.

EEG recordings from identical (monozygotic) twins, including those reared apart, show the same degree of similarity as repeated EEG recordings taken from the same person on different occasions (e.g., Bouchard, Lykken, McGue, Segal, & Tellegen, 1990; Stassen, Lykken, Propping, & Bomben, 1988), suggesting that individual differences in the EEG are almost solely determined by genetic factors. Heritability estimates obtained in a family study of the EEG

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(Anokhin, 1987) were consistent with results from twin studies, suggesting that manifestation of genetic factors in the EEG is similar in twin and nontwin populations.

Our own genetic studies of the EEG have been characterized by large samples and the use of model-fitting approaches, in which a large set of EEG parameters is analyzed simultaneously (multivariate analyses). Multivariate genetic analyses can reveal whether two or more variables have a shared genetic or an independent genetic basis. Both twin (van Beijsterveldt, Molenaar, de Geus, & Boomsma, 1996) and family (Anokhin, 1987) studies using this technique suggest that the individual variation in EEG from a large number of different brain areas is strongly interrelated and largely reflects the expression of the same genes. These findings testify to the existence of genetically determined neurophysiological differences that manifest themselves at the whole-brain level.

Another feature of more recent studies is the use of electrophysiological indices that are more meaningfully related to behavior, such as EEG coherence and ERPs. EEG coherence is a measure of synchronization of activity in different brain areas that is widely used to study the organization of brain functioning. EEG coherence is a promising tool for the study of individual differences because complex behavioral traits, like general intelligence, are likely to be related to individual differences in organization of brain activity, rather than to the characteristics of activity at isolated cortical sites.

A few recent studies (Ibatoullina, Vardaris, & Thompson, 1994; van Baal, de Geus, & Boomsma, in press-a) have indicated that the genetic influences on EEG coherence are greater for connections within a hemisphere than between hemispheres and are greater for long-distance connections than short-distance (local) connections.

ERPs representing the response of the brain to external and internal events also show substantial genetic influence, although heritability estimates are generally lower than for spontaneous EEG activity. For the amplitude of the P300, heritability is around 50% in most studies, but a wide range of values is reported. A heritability of 50% means that 50% of variation across individuals can be attributed to genetic factors, leaving 50% for shared (e.g., within the family) or unique environmental factors. For P300 latency, heritabilities vary even more widely. The large variation in heritability estimates for ERPs may be due to the use of many different tasks to evoke the ERPs.

This issue was addressed in a series of Russian twin studies investigating genetic influences on ERPs elicited in a variety of experimental paradigms ranging from simple sensory stimulation to complex cognitive tasks (summarized in Ravich-Sherbo, 1988). The degree of heritability for ERPs turned out to be relatively independent of stimulus modality, but was related to stimulus intensity. With few exceptions, genetic influences were stronger for the responses to stimuli of higher intensity. Furthermore, heritability of ERP components was related to stimulus properties. ERP responses to more elementary stimuli, like light flashes, showed a greater genetic component than ERP responses to stimuli bearing semantic content. And, finally, ERP heritability depended on the role of the stimulus in the entire task context. When the subject's attention was drawn to the stimulus (e.g., counting stimuli) or distracted from the stimulus (e.g., performing mental arithmetic), heritability was higher. As a general explanation for these results, Ravich-Sherbo (1988) proposed that a higher background level of general nonspecific arousal makes genetic differences in information processing more salient. This last suggestion is consistent with a recent finding of a higher ERP heritability in difficult than easy tasks (Katsanis, Iacono, McGue, & Carlson, 1997). Studies involving twins of different ages found a higher ERP heritability for the same task in 5-year-old children than in adolescents (van Baal, de Geus, & Boomsma, in press-b; van Beijsterveldt, Molenaar, de Geus, & Boomsma, in press). Because the task was difficult for the younger group and easy for the older group, these results also suggest that heritability of brain activity increases with increasing task difficulty. These results seem to indicate that genetic differences in brain function are most salient in situations requiring maximum mobilization of neural resources.

It has sometimes been questioned whether the high similarity of identical twins in EEG parameters could reflect similarity in their skull shape. Dustman and Beck (1965), in one of the first studies of twins' ERPs in response to visual stimuli, showed the correlations between twins were not affected by the large similarity of identical twins for head length and width nor by little changes in the placement of electrodes. Also, the differential heritabilities for ERPs observed under different task conditions would be hard to explain based on twins' similarities in skull shape.

Taken together, these studies indicate that individual differences in electrical activity, both spontaneous and elicited by specific stimuli or tasks, are strongly influenced by genetic factors. This is a fundamental conclusion that raises a new question: What specific genes are involved?

GETTING CLOSER TO GENES

Although EEGs are commonly described in terms of quantitative traits, EEG researchers have also distinguished variants that are characterized by specific patterns of electrical activity. Family studies suggest that some such variants are genetic in origin and can be transmitted in families very much like eye color or blood groups (Vogel, 1970). One of these variants, the low-voltage EEG, is characterized by the absence of alpha rhythm (8–12 Hz), usually the most salient component of the human EEG. Studies of behavioral correlates suggest that this pattern of brain activity is associated with emotional instability, decreased concentration, poor adaptation to extreme conditions, anxiety, and increased risk for a specific subtype of alcoholism associated with anxiety. The existence of such a well-defined EEG pattern with a simple mode of inheritance provides a remarkable opportunity to search for the responsible gene.

The chromosomal location of a single gene influencing a particular trait can be determined by establishing a genetic linkage between the trait and a genetic marker. A genetic marker is a DNA variant with a known chromosomal location. A very large number of such markers have become available in the past 10 years. If a trait under study is inherited together with a particular DNA variant in families, this indicates genetic linkage: A putative gene responsible for the trait is located on the same chromosome close to the marker. Linkage analysis of the low-voltage EEG suggested that a gene responsible for this specific pattern of brain activity is located on the long arm of Chromosome 20 (Anokhin et al., 1992; Steinlein, Anokhin, Mao, Schalt, & Vogel, 1992). However, the analysis showed genetic heterogeneity of this trait; that is, this gene underlies the low-voltage EEG only in some of the families, whereas in other families, other genes with different chromosomal locations may be involved. Findings like this are typical for the analysis of complex traits that are likely to be due to several or even many genes.

A large-scale effort to identify single genes underlying variability in electrical activity of the brain is being undertaken as part of the Collaborative Study on the Genetics of Alcoholism (Begleiter, 1996). This initiative was motivated by the fact that a low P300 amplitude is associated with increased genetic risk for alcoholism. Begleiter and his group demonstrated that the deviant P300 actually precedes the development of alcoholism and is present in individuals at high genetic risk for developing alcoholism. Previous multivariate model fitting (van Beijsterveldt et al., in press) had suggested separate genetic influences on the P300 amplitude recorded above the frontal, executive areas of the brain and above areas in the back of the brain engaged in sensory processing. Preliminary results of Begleiter's (1996) ongoing research now suggest that several genetic loci on Chromosomes 2 and 6 are involved in determining P300 amplitude, and that different loci do indeed influence brain activity in the frontal, executive areas and the sensory-processing areas.

If a candidate gene is implicated on theoretical grounds, genetic association studies can be employed. In association studies, alleles at a candidate locus are compared between groups. (Alleles are alternative forms of a gene at a locus.) Groups known to differ in a crucial trait are compared with respect to the frequency of certain alleles. Noble, Berman, Ozkaragoz, and Ritchie (1994) used this approach to study the effect of a dopamine receptor gene (DRD2) on latency and amplitude of the P300 in a sample of 14-year-old Caucasian boys. Evidence from pharmacological studies had already suggested an involvement of the neurotransmitter dopamine in P300 latency. Because the effects of dopamine in the brain depend strongly on the number and structure of dopamine receptors, a gene known to influence the dopamine receptors seemed an excellent candidate. Confirmation of the role of the dopamine receptor gene was found when Noble et al. observed a significantly longer P300 latency (43 ms, or 10%) in boys carrying alleles of type A1 compared with boys who had alleles of type A2 only.

Finally, Freedman et al. (1997) have reported linkage between a marker on Chromosome 15q and inhibition of the P50 response to repeated sound clicks. The P50 is an early auditory ERP component whose inhibition was previously shown to be associated with schizophrenia. Although linkage cannot show exactly which of the approximately 350 genes in the targeted region is associated with an abnormal P50, there is good reason from animal research to suspect the gene for a particular nicotine receptor (the alpha-7 receptor). If the mutations responsible for the linkage are identified, their neurobiological effects throughout the brain can be tested, providing valuable insights into the pathophysiology of schizophrenia.

CONCLUSIONS AND FUTURE DIRECTIONS

We have tried to show that genetic analysis at an elementary level of brain physiology may increase the chances of identifying specific genes that influence com-

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plex behaviors. In some cases, it may be useful to aim the genetic analysis at neurophysiological traits associated with disorders, and with genetic risk for disorders, rather than at the disorders themselves. The efficacy of this approach is illustrated by some early results of linkage and association studies of EEG and ERP indices in the genetic research of alcoholism and schizophrenia. These encouraging results are, of course, far from conclusive, and await replication. However, they demonstrate the utility of genetic psychophysiology in the elucidation of gene-brain-behavior relationships.

The experience of psychiatric genetics over the past decade should be noted in any discussion of the utility of linkage studies. Large efforts have been made to map the genes responsible for major psychiatric diseases, and the first results were encouraging. However, after a series of failures to replicate initial findings, the excitement gave place to skepticism. At this moment, it is difficult to predict whether the efforts to find genes affecting brain physiology will prove more successful than linkage studies of psychiatric diseases and normal behaviors. Nevertheless, it is clear that the two approaches are complementary to each other and, taken together, can provide a coherent picture of how genes influence complex behaviors.

Of course, finding genetic linkage is only the first step in unraveling the mechanisms underlying a particular behavior or trait. Advanced molecular genetic techniques must now be used to help find specific genes and the brain areas where they are expressed. Animal models, in which a target gene can be disabled to study its effect, and drugs that specifically affect the neurotransmitter pathways on which the gene has an influence can both clarify the function of genes in the generation of electrical brain activity. Psychophysiological studies can then readdress the brain–behavior relationship, focusing sharply on the EEG parameters for which genes have been found. Even when a gene-brain-behavior link will not be readily apparent from genetic linkage results, finding genetic markers for electrophysiological measures will always provide an excellent starting point for further research.

Notes

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2. Fourier analysis is used to study complex signals that result when many different waves with different characteristics are summed to yield a single signal. This mathematical technique can be used, for instance, to describe the specific timbre of a clarinet as a specific combination of the sound waves making up its sound.

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